Castro, Oswaldo 2001

Dr. Oswaldo Castro Oral History 2001

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Interviewer: Valerie Williams

Williams: First of all, I would like to thank you for meeting with me. I appreciate the time that you spent with me to talk about historical aspects of sickle cell disease research. I'd like to start off by asking a little bit about how you got started with sickle cell research, what was sort of the first research project you did related to it and what was the hypothesis of that research.

Castro: We got started on sickle cell research back in 1972 to '74, and at that time my mentor at Yale University, Dr. Stuart Finch, had devised an animal model for looking at the intravascular survival of human sickle cells transfused to those animals. Normally, when one transfused red cells from one species to another, the red cells are immediately taken out of circulation. The differences immunologically are so great. But he then devised a way to block the animal's immune system in such a way that, at least for a day or so, the human cells would be able to circulate in the animal. And then we were looking for what type of disorders to start using the model for, and, of course, we thought of sickle cell right away because we know that the red cells from sickle cell patients have a low survival in the blood of the patients, and we were able to demonstrate that they also had a low survival in the rats when compared to normal red cells. And then, based on that, we were able to make some observations having to do with whether or not even the animals' oxygen would cause a greater or more rapid clearance or less rapid clearance of the red cells that were transfused and whether or not the various experimental drugs or procedures could be used in that model. So that was the gist of it.

Williams: Okay. So we were looking at the survival of red blood cells in animal models.

Castro: Right.

Williams: Now, at this time -- and I'm following a time line, creating a time line here, the research that went on after Pauling. So my understanding is, around 1972, urea therapy had been tried and we were now into cyanate therapy, the idea that it was carbamylation that was responsible for increased survival of the red cells.

Castro: Right.

Williams: So did you do experiments with carbamylation?

Castro: I would have to have my CV to see whether or not I published anything. My recollection is that we did the survival of carbamylated red cells and we found them to be improved as opposed to the non-treated cells. But I'd have to look at the CV. This is, you know, I wouldn't say ancient history, but it's a long, long time ago. So, yes, we were doing experiments such as that.

Williams: Right, okay. And so that was at Yale, and so with . . .

Castro: We continued that work here. In 1974, I became a faculty member here at Howard University, and from then on, I did, I'd been doing primarily sickle cell treatment or sickle cell research, almost exclusively, actually.

Williams: Oh, okay. So you'd been treating patients, doing the research as well. Okay. I brought my questions just to keep going.

So, as you were working on carbamylation, because what I'm trying to put together is how the different strategies evolved, so one strategy was to increase the oxygen affinity of the red blood cells. They would have a survival rate. What eventually happened to that strategy as far as you remember?

Castro: Well, it actually was tried in human beings, in sickle cell patients, and it appeared to work. However, it had side effects because the cyanate carbamylated other proteins, and as I recall, the people got cataracts, and there may also have been neuropathy. So, therefore, for that reason, even though there was some promise to the carbamylation, that particular strategy was abandoned. I stayed on it for a little while longer because what I wanted to do was to take out the patient's red cells one unit at a time, carbamylate them in vitro, then freezing them, and then the idea was, if one were to then transfuse those carbamylated cells, once you wash away excess cyanate, then you would have no carbamylation. You'd just have treated cells. And we did experiments like that in both humans and in rats, and we did show that even frozen carbamylated cells had a better survival in human beings than their own red cells when they were fresh. So we thought that was interesting. But it was basically not very practical because then you would have to be taking blood in large quantities and store them frozen, and the patients were anemic, so they didn't have too many red cells, so it was interesting, but it just never became practical.

Williams: Because this would have been a preventive treatment; that is, you would have, you would do this to prevent sickle cell crises?

Castro: Well, I was thinking it was more like a treatment. If a patient, for example, became severely anemic, the blood count was very low, rather than giving the patients red cells that don't sickle but they are from somebody else, you could give a patient's own red cells that do sickle, but they sickle less than the fresh ones. So this was the idea. But the logistics of it were pretty horrendous. To accumulate enough red cells, you have to have a whole blood bank just waiting for you. So it was a nice theoretical idea, but I don't think practically it had much chance.

Williams: Okay. So, who were some of the collaborators that you were working with during this period on some of these ideas?

Castro: On this idea specifically, or in general?

Williams: I guess I mean with some of your carbamylation work earlier. We'll move to more recent research, but just sort of in the beginning, after you left. You were with Stuart Finch at Yale.

Castro: Yeah. When I was here, I was working under Roland B. Scott, who founded the Sickle Cell Center, and so we worked in collaboration with him, supported both my research and supported me in doing that.

And we had also, when we were doing the freezing experiments, we had collaborated with Dr. Merriman at the Red Cross Research Laboratory. And he and other people there taught me how to do the freezing and how to be able to freeze the red blood cells without losing them in the process.

Williams: Oh, how interesting. Okay. So you did work with Dr. Scott for a number of years?

Castro: Oh, yeah. Well, he was my boss until he retired in 1990.

Williams: I see. Okay, then. I guess I missed an opportunity to interview him.

Castro: He retired in 1990, but he has been in very frail health since then.

Williams: Okay, okay, then. I don't think I was aware of that. So, this is the 1970s. This was around the time that there was legislation for sickle cell and the development of the sickle cell centers. What was the climate like at that time? Were people optimistic about getting cures at this time? Or was there a sense of treatment right around the corner?

Castro: Well, that was the case, and particularly since it looked as though the federal government was finding, demonstrating tangible interest in the disease. There was the Sickle Cell Anemia Control Act passed in '71 and then again in '75, and they authorized initially the appropriation of $25 million per year back in the '70s.

Williams: Oh. That's a lot of money.

Castro: So that they, this resulted in the creation of federally funded sickle cell centers that were comprehensive in that they took care of the patients, they did education, counseling, community outreach, and, of course, research.

Williams: Right. And prior to the centers being developed, do you think that there wasn't as much focus on sickle cell? Do you think they needed focus? I mean, obviously, they felt they needed to do it. Could you maybe talk about that a little bit?

Castro: I don't have firsthand experience, but based on what was published in those days, it seems to me that it was being investigated in relatively few places, whereas once it became a disease that there was a special focus on, like with the sickle cell centers, then a lot of people applied for funds. And you had to apply for funds to have to have some preliminary data. So I think they opened up the possibilities for more people to become involved in sickle cell research.

Williams: Okay. Do you know how the centers were selected?

Castro: They were selected by a regular peer-review process at NIH. It was a very involved process, so involved that it took two years from the time that we wrote the application to the applications were funded, two years, and there were, at least initially, there were site visits in which people came, 10 to 20 investigators came, peer reviewers, to site-visit the various centers. And then based on that, they had an initial review of the center, and then, based on that, they had another tier of review, and then they selected 10 or 15 centers, depending on the amount of money that was available.

Williams: And do you know what they were looking for in terms of their criteria?

Castro: Well, we knew that because that was always expressly written in the request for applications or RFAs, and they were looking for a comprehensive program, meaning that you did have to have some education. For a while, you did need to have testing as a community testing. You always have to have good patient care, and you always have to have research. And the research could be both on the basic level, molecular or cellular or animal or clinical research or psychosocial research. It would be very broad. And, obviously, the various sickle cell centers had different types of research projects. Some of them would be more specialized in one type of research than others. Now, in terms of the criteria, once it was determined that the center was a viable center because it had the patients, it had the education, and all that, then, in terms of how they are selected, they were selected in great part by the peer-review assessment of the research. So that everything else being equal, if you have better perceived research, then you have a better chance of becoming funded.

Williams: I see, okay. Quality of the research.

Castro: Exactly, exactly.

Williams: Okay, all right. And within these centers, do you feel like the historically minority institutions had a special role to play?

Castro: Initially they did because the center program was, at least initially, thought to be part of a national project, so that geographically, they didn't want all the universities to be centered in one place. They always put a little bit of geographic distribution. And in at least two of the RFAs for the various competitions that took place every five years, in at least two of them, I remember that they specifically intended to fund at least one minority institution. In the last two competitions, they took it out.

Williams: Oh, really?

Castro: Yes. So even though they may have intended to fund it, they did not explicitly say that they would. And, as a matter of fact, since, in the present competition, which started in 1998-2003, there isn't any minority center.

Williams: Really?

Castro: Yes. Although up to that time, there had always been one, either Howard University or elsewhere.

Williams: Right. Any ideas as to why that happened?

Castro: Well, first of all, the rationale for having a minority institution is that minority institutions would have either access to more patients or would have a better relation with the community, that they would be able to get better cooperation from the patients, and that sort of thing, and, of course, because it was felt to be [a disease] that affects predominantly African-Americans, so it seemed logical to do everything possible to fund research at such institutions. As to why it is that it was then later on removed, that was never explained.

Williams: Okay, all right. At least at one time it was a focus.

Castro: Well, it was because they said specifically in the RFA that they intended or wanted to fund minority institutions.

Williams: Okay, all right. Let's move a little bit to these treatments. Now, I know, well, I don't know. Maybe you can explain to me, how do we get to hydroxyurea? We were looking. It seems like the research was focusing on making modifications to the sickle hemoglobin red cells. But was there always a body of research, as far as you know, that was concerned with increasing the synthesis of fetal hemoglobin?

Castro: It was always a wish, a wish that one could increase fetal hemoglobin, because very early on it was found that (a) the children who were born with sickle cell disease had no symptoms as long as they still had fetal hemoglobin. It was only when the fetal hemoglobin decreased in concentration in the blood that they began to have symptoms.

Williams: Right. And that was a natural decrease with aging.

Castro: Right. It happens in all of us, right, I mean within the first year. So, in addition to that, there were interesting observations from sickle cell patients from the Middle East, Saudi Arabia and India, in whom they naturally have very high levels of fetal hemoglobin. For example, most African patients have about 5 percent fetal hemoglobin. The Arab patients or Indian patients have about 20 percent.

Williams: Oh, wow.

Castro: And it was always known that those patients had a milder disease, so everyone knew that if one could increase fetal hemoglobin, then one could achieve an improvement in the patients. And the reason for that was also found out by the research mainly that, in contrast to the other hemoglobin, hemoglobin A and C, fetal hemoglobin would not take part on the hemoglobin so that it will serve in a way as an inhibitor. One calculates that if you have 20 percent fetal hemoglobin in each cell, in each cell, that there will be no sickling in the body. There could be sickling in the test tube, but not in the body. And that's information that was also derived not only from in vitro tests, but also from patients who have high fetal hemoglobin levels and have about 20 percent fetal in each cell. It's called sickle persistence of hemoglobin, and those patients have no symptoms. So there was a lot of evidence pointing that increasing fetal hemoglobin would be good. And then, I think it was in the late '70s, early '80s -- I can't remember exactly when -- there was a doctor, there were two doctors, Dr. Heller and Dr. DeSimone, and they were at the VA hospital in Chicago. And they had the idea that or they have noticed that when you stress the bone marrow, like when you make the, when an individual, a human individual became very anemic and the bone marrow started making cells again, some fetal hemoglobin was produced which was more than what it would have been. As I recall, they then went to baboon models, and they either made them anemic by reducing the life span of their cells with a chemical or by simply bleeding them so they would become anemic. And they noticed that as they became anemic from the stress, their fetal hemoglobin went up. And this is the most important thing -- when in addition to that, they gave an anti-cancer drug called 5-azacytidine, then the fetal hemoglobin went even higher in those animals. So that's what started the whole thing rolling. Everybody knew that we needed to have increased fetal hemoglobin, but nobody knew how to do it. Okay? And the way that this is going, soon afterwards, it was found that the same thing happened in human beings with sickle cell anemia, and that not only could 5-azacytidine be used for that, but other chemotherapy and hydroxyurea urea. In the '90s, in the late '80s, early '90s, hydroxyurea was chosen as the drug to try because it was easy to give. It could be given by mouth in contrast to the other drugs, by intravenously, and because hydroxyuurea was not known to cause cancer, or leukemias. A number of other anti-leukemic drugs can in the long run themselves lead to cancer, but it has never been shown for sure with hydroxyurea, so that's how it got started.

Williams: I see. That's so interesting. Azacytidine.

Castro: 5-azacytidine.

Williams: Right, 5-azacytidine.

Castro: Now, Dr. DeSimone, if you can interview him, his work, he was right at ground zero, at the very, or the ground floor when this whole thing started.

Williams: Yes. It would be interesting how he came upon that particular chemical agent to try. I mean, was it by happenstance? I wonder. Did he have some inkling?

Castro: He had some inkling. I'm sure he'll talk to you. But I think that the idea is that if you stress the bone marrow, then when the bone marrows re-expands or expands more, you end up having more fetal cells than before.

Williams: Yeah, that is something. So that sort of spawned a whole new body of research, if you will, and so people really stopped focusing on ways to modify sickle red blood cells or increase oxygen affinity. Are those strategies still out there?

Castro: Well, there are other strategies that are still very much alive, and that is that there are, for example, investigations that showed that the red cells in sickle cell disease tend to stick to the endothelium of the blood vessels, and when they stick there, then they are more likely to form polymer and to sickle, so that if there was a way to somehow be able to decrease the interaction between one cell with the other cells sticking together, endothelium, then that would be beneficial. And, in fact, just very recently, a paper came out about a substance called poloxamer 188, which, if given intravenously, you're in a crisis, significantly decreases, statistically significantly decreases the duration of the crisis, even though that decrease is not very much. But it does have some. So it points the way that there may be some way, some other way, or a different way, a different dose, and so on, so I think that's encouraging. There have been some substances, chlorpromazine, for example, which has been shown to increase the water content of the red cells. And, of course, when you do that, then you decrease the concentration of hemoglobin S, and that would cause less sickling, so that there is reason to believe that a compound that acts like that could be used as well. Therefore, there are different ways of attacking it. One of them would be to increase fetal hemoglobin, and it doesn't have to be necessarily by a drug. It could be done by some genetic mechanism once people discover what is the precise mechanism of the switch. Maybe we can prevent the switch and you have a much higher amount of fetal hemoglobin, which would constitute a cure so that is one thing. The other thing would be to try to decrease the interaction between the cells and the endothelium, and the other one would be to put in more water inside the cells so they would not sickle or polymer or would not polymerize as much. So all of these things are very exciting, and it is somewhat ironic that they are occurring precisely at a time when the funding for sickle cell is becoming less rather than more.

Williams: Well, that's interesting. One of the things interesting about sickle cell is that it was, almost got its start in the clinic. It was a clinical diagnosis of a particular condition, and it spawned a whole area of research, basic research, on protein structure, hemoglobin structure, function, that sort of thing. Do you think that in some ways the focus got diverted, people got more into sort of the basic research structural questions and lost focus on developing treatments at some point? Or maybe recently it's kind of gotten back to the treatment point?

Castro: Well, I can maybe read you something that I talked to a congressional black caucus in February of this year. I said that a lot of other diseases and conditions have benefitted from sickle cell research, but, as you say, once it became known to be a molecular disease, it often got all this stuff. For example, I said that the Human Genome Project has benefitted greatly from knowledge that was initially provided by sickle cell disease. We said we often forget that molecular medicine and modern molecular genetics began with the concept of sickle cell anemia as a molecular disease. I said that progress in molecular genetics is impressive and has contributed to better understanding and treatment of many other medical conditions, including cancer and HIV disease. Furthermore, molecular genetics has advanced our knowledge in the diverse areas such as forensic medicine, evolution, anthropology, history, all of this, from initial molecular genetics from sickle cell disease. I said, "It is ironic that so far the sickle cell patients themselves have not enjoyed the benefits from those scientific advances." So that's something that I'm on the record for having said.

Williams: Okay. Well, thank you for sharing that. But certainly that is one of the controversies that I've come across in the literature; that is that a lot of people, a lot of literature points to the fact that, at some point, the focus was less on developing treatment for these patients and more on developing these new areas of research and asking the basic fundamental research questions, which to some extent certainly did further the research, no question about that. But I think there is a sense of balance that's in question.

Castro: I think that's the correct approach because I don't think there's anything wrong, and so much knowledge to be gained. Everybody benefits. But I do think that we should have remembered who was it that initially had the disease and everybody else seemed to be benefitting, and they have been much slower. So I think that it is for that reason that I've felt and I've always felt that, although I don't have any proof, that the funding for sickle cell disease allowed for inflation has actually collapsed rather than expanded. And that's why, if any advances of sickle cell research that you see there were done with very little, relatively speaking, and it could be that one would be able to analyze simply the human impact of sickle cell disease, one can do that in dollar amounts and see whether or not the amount of research dollars that are going to disease is appropriate to the degree of suffering of the people.

Williams: Well, you know, and I thought about that because, like I said, I mean, inasmuch as I'm looking at the history of sickle cell research, I' m looking at that, looking at the factors that influenced the progression of research on this disease and treatment. And I wondered at some point if the federal funding has a role to play in this. But I also wondered if there would be -- I could possibly look at a parallel disease like cystic fibrosis, thalassemia or something, and look at perhaps a disease that has a similar origin, perhaps strikes a different population. And would comparison like that be fruitful? I mean, I know that, at least from the literature, people often think of cystic fibrosis, similar profiles, a molecular disease, and yet the thought is much more has been done.

Castro: I don't know. I don't have firsthand information on that. But I can tell you this. There was a recent article -- recent, a couple of years ago -- in the *New England Journal of Medicine* in which they actually correlated the amount of public health importance of disease and the research dollars from NIH, and there was no correlation.

Williams: There was none.

Castro: No. Some disorders that had a lower impact were overfunded, quote unquote, if you want to call it that. Nothing's really overfunded. And some other ones that appeared to have greater impact were underfunded. And you maybe will find the article on the Internet somewhere, but I thought that was very interesting. And a number of disorders were listed there, and there were graphs and everything, but sickle cell didn't even make the grade. It wasn't even mentioned. It was interesting because it is a disorder that has a specific minority constituency, and compared to all the others, cystic fibrosis, sickle cell is quite common, certainly more common than thalassemia.

Williams: Right, right, exactly, which has, I think, a much smaller affected population, but you hear quite a bit about that.

Castro: Yes. You do have more community and private groups advocating for than for sickle cell disease. There is one Sickle Cell Disease Association, which is a national organization, but every big city has some association as well.

Williams: Right. I was going to ask you about that. What do you think the world of political advocacy has done for sickle cell? I know, like you said, there is the SCDAA. I think that's the acronym for the national alliance, and their local chapter is in D.C. as well. Is that where you think perhaps more attention could have been paid to political advocacy for the disease?

Castro: I don't know.

Williams: You don't know.

Castro: I don't know. I do know that there should be more attention from the government, from Congress, to this disease. I think that, for example, there's no reason to fund only 10 centers. And although I cannot see how they could fund more, since the total amount, in my view, keeps on contracting. You may able to find that in the NIH somewhere, you know, the center program budget, and look at it in constant dollars. I can tell you that our own budget, because we used to be a center a long time ago, I mean, we were a federally funded center, the budgets that were in the '70s and '80s compared to what we had later on really didn't compare. They stayed the same or became lower. At least that's our opinion of it. So I would look at those things for hard data. I would look at the yearly amount spent on sickle cell centers, sickle cell program budget, and compare with inflation. That would be one way. The societal impact of sickle cell disease in terms of number of people affected and how much they suffer and how much they don't work or whatever, and the amount of research money that goes to it, and see where they are in the line or they're way above or way below.

Williams: Right. That's an excellent idea.

Castro: If somebody were to do that, it would really be a big eye-opener, and people would know, and something maybe would happen.

Williams: Yeah. I think that's an excellent idea. Is there any private-sector funding for this?

Castro: Very little, very little. I don't know of any large corporation or conglomerate that has given the types of monies that would be and in stable amounts that would be necessary. I don't think we have a muscular dystrophy type of program in which you have a very public funding base. So we are in need of community-based fundraising for research in general.

Williams: Okay. But at this point, the major sponsor for much of the sickle cell research is, say, NIH at this point.

Castro: Yeah.

Williams: And are there other federal agencies?

Castro: There have been some drug companies that keep on trying to find drugs that might benefit the patients, and basically their interest is that, in my opinion, once they see that they are good for sickle cell because they allow blood to flow better, maybe they will get used for myocardial infarction and stroke. We have a much bigger market. I mean, that's what I'm saying because there's that possibility. These are pharmaceutical companies. They do research and they need to think how they get their money back.

Williams: And they're probably thinking they don't have a big enough demographic population just among sickle cell to get the money back for the R&D.

Castro: No doubt. The FDA and federal government does have, they call it orphan drug type research, where they allow universities and I think also companies, pharmaceutical companies, money to develop drugs for disorders that don't affect very large numbers of people.

Williams: Okay, right. But that is a sort of special program.

Castro: Special program. It's not a lot.

Williams: So, what about the cooperative study of sickle cell disease?

Castro: Well, that was funded, and I don't know exactly whether it was from center funds. I doubt it. It involved other institutions. And that started back in '79. We were a part of that. And it ended eventually in the '90s. So there is a lot of data which is available for research so that people can understand better, there are correlations between this factor and that factor, and that way learn more about how sickle cell disease affects people and what are the more severe risk factors and the like. So that was a good thing.

Williams: It was, in your opinion. It added a lot to the body of information.

Castro: Right.

Williams: At this point I wanted to ask you a little bit about the quality of life for a typical sickle cell patient. What sort of treatment do they get on a regular basis? You know, if a patient comes in to you, what are some of the symptoms that you see, what does the patient look like?

Castro: It's quite variable. There are children with sickle cell disease, young children. I see young and old patients. And both within the children and within the adults, there is a great deal of variability in terms of how severely affected people are. There is a relatively large proportion, maybe about 30-40 percent of patients, that are only rarely symptomatic. They get a complication like pain crisis. But there is another, at least among adult patients, there is this small population of patients, about 15-20 percent, that are sick very, very frequently. These are people who are very ill all the time. And it is that type of patient that generally will come to our clinics and try new things. And the hydroxyurea study was a clinical trial in which those patients were eligible. We specifically wanted to test people that were more severely affected. People, in order to be eligible to try hydroxyurea, had to have at least three crises per year.

Williams: And define a crisis for me.

Castro: A crisis is a relatively sudden onset of pain, usually in the bones of the extremities, but it can be also in the back or in the abdomen, and it is thought to be due to the poor flow of red blood cells in the microcirculation as a result of sickling or polymerization.

Williams: I see. And how long do these episodes last?

Castro: Quite variable. The average hospital stay for children is on the order of five days, for adults it's on the order of seven days average. And if you have a vascular occlusion involved in not just the bones but also the lungs, for example, you have a second common problem called chest syndrome, and that is more severe. It has a mortality of anywhere from 5 to 9 percent. And the length of hospital stay in adult patients may be 12 days or higher.

Williams: Okay. So, when they're in the hospital, how are they being treated? What exactly are they being treated for?

Castro: It depends on what is the major problem. They all have pain, so pain management is the major reason why they come into the hospital. But if they develop what we call this chest syndrome that I talked about, then, of course, things become different. In addition to the pain, they may not have enough oxygen in the blood, and they need to get oxygen. The blood doesn't flow well to the lungs. We may need to have a transfusion with normal red cells that will flow better to the lungs, and that's how they are treated. Sometimes they have infections and need treatment for that, too.

Williams: Is it common for people to just come in for pain medication and leave without hospitalization?

Castro: Oh, yeah. A number of people who have not as severe pain crisis will either come to the doctor's office or to the emergency room, be examined and treated for a few hours, and then leave.

Williams: One of the reasons why I asked this is because I've been reading that there's instances of abuse with pain medication, so I was wondering, for patients who did not (a) come in for hospitalization, (a) were they likely to be misdiagnosed, (b) how sympathetic are doctors to giving pain medication to patients, and is that another issue related to this?

Castro: Well, that's a general issue, not only for sickle cell, but in all painful conditions. There is evidence that there is an almost widespread under treatment of pain, and the reason given is that the doctors are concerned that (a) the pain medication given at a very strong dose may harm patients, either quickly in that they will have a lower rate of breathing suppression, or, in the long run, if they become used to the medication so they become tolerant and need higher doses and so forth. There is also a confusion in the medical profession and nursing profession about the difference between addiction and dependency. People who have a medical condition and are dependent on a certain treatment are called just that; they are dependent. Like if people have diabetes and they need insulin, they are insulin-dependent. And if people have renal failure and they need dialysis, they are called dialysis-dependent. But if you have pain and you're dependent on narcotic medications, you are dependent, but you may be viewed by somebody who doesn't know as being addicted, so more education needs to be done in order to be able to address that problem. That's not to say that there is no actual addiction, because there is no protection from addiction by sickle cell disease. The best preliminary information that we have is that the self-report of drug abuse -- and by that, I mean marijuana or cocaine -- is no higher in the sickle cell population than in the general population. So there is such a thing as addiction, but we tend to call that when you're dealing with things like cocaine, PCP, or marijuana, and also heroin, all these sort of things. And it's also possible to be addicted to the narcotic medication as well.

Williams: Okay. So, given some of these medications and treatments, what is the quality of life like for a sickle cell patient? I mean, can they pretty much live, I don't want to say normal, but a fairly routine life? Is it constantly interrupted by having to come in with hospital visits?

Castro: The patients are extremely resilient. Many of them, as soon as the pain is gone, they will act normally, will go back to their jobs. Many of them are incapacitated, at least are unable to keep jobs, because they just got a job and then two weeks later they developed a crisis, they' re off, and then the employer cannot accommodate that, so they're released. And so that is a problem. And, obviously, there are other patients, a few of them, in whom the pain is, episodes occur almost every day, and, of course, their quality of life is very poor.

Williams: But in terms of the mortality due to sickle cell?

Castro: Well, the mortality, based on the cooperative study that you asked me about earlier, has been determined, and the data on which the mortality was determined, however, is data from the '70s and from the '80s. And based on that data for SS patients, which is the more severe form of sickle cell disease, the mean survival for males was 42 years and the mean or median survival for females was 48 years. So it was practically the fifth decade that they succumb, so that sickle cell anemia reduces life span by about 20 years. And when, of course, you talk about median survival of 48 years, it means half of them die before that age. And, of course, that is quite tragic. Now, what that median survival is nowadays, that's very hard to pin down for two reasons. Number one, we now have better medical care. We know what to be treatable, like, for example, stroke that can now be prevented, like this chest syndrome that has also be, not prevented, at least it can be treated, things of that nature, so that all those things tend to increase the patient' s life span, on the one hand. On the other hand, since the same interventions are being done in children, now we see that children that normally, before better treatment, would have died in infancy, they are now surviving and they're becoming the more severely affected adults.

Williams: Oh, really?

Castro: Well, yeah. That makes sense. So we expect that we will get a crop of, a cohort of sickle cell children that we didn't used to get before because, unfortunately, they had died. But now that they have better treatment, they will survive, and their particular problems will become manifested in adulthood. So it's very hard to pin down as to whether or not the mortality is now better or worse than it was before.

Williams: Right. But they will have more severe symptoms.

Castro: Well, it stands to, it has to be proven. I haven't seen any studies. It stands to reason that if before better treatment, we used to have as much as 30 percent mortality in infancy, in childhood, as much as that, now we have, at the most, with good medical care, 5 percent mortality, so that all these young people will become adults, and that's good. But some of the more severely affected than normally, at least in the past, have died will now survive, and there is reason to believe they will become severely affected adults. And for that reason, I think that the improvement that hydroxyurea could bring and better treatment could bring could be offset by the new, more severely ill patient. But, I mean, this is just my opinion. I haven't seen data.

Williams: Well, I guess one of the reasons why I wanted to follow this line of thinking is that I wonder if the perception about the urgency of the need for a cure has somehow been mitigated in the sense that people are saying, "Well, the mortality is down, people are living longer." Questions about the quality of life aren't being asked necessarily, but certainly you do see significant progress. So perhaps the urgency isn't there as it was at one point. Right now I know that bone-marrow transplantation is supposedly seen as a very promising one, but there are many problems with that right now. So, just in terms of funding, the urgency for cure perhaps is lessened, and I wondered about that.

Castro: All I can tell you is what I see. What I see is that the amount of money allocated for the centers, research centers, is no better now than what it was 10 years ago.

Williams: Well, certainly research on sickle cell isn't limited to the centers.

Castro: It's not. You may be able to get funding for research somewhere else, but if you do not have a patient population, like in centers which do research, then it'll become more difficult to get preliminary data to be able to do the types of research that we want to do, so that, yes, there are other people doing other things. As a matter of fact, the whole bone-marrow transplantation research was piggybacked on bone-marrow transplantation for leukemias without much in the way of funding from the sickle cell problem. Now bone marrow transplantation is something that is very promising. But so far the promise is limited to those who have a sibling. That's only 10 percent of people. And only those who have not been affected that much by sickle cell, in other words, young children, bone-marrow transplant of adults doesn't seem to work, so that there are problems with that. And certainly more could be done to be able to bring bone-marrow or core blood or stem-cell transplantation more research, but those are so expensive that you could not do it from the centers. You would probably have to do it from already existing transplantation facilities.

Williams: That's interesting. You could not do them from the centers.

Castro: Well, it's a very expensive thing. You would have to have the patients be transplanted in larger numbers. However, centers could collaborate with the transplantation units.

Williams: Right. Is there a lot of collaboration among the centers?

Castro: Yes. That's built in in the sense that they're supposed to meet every year and discuss their findings. They're supposed to provide reports as far as their research every year, they also collaborate in research programs among themselves, and also with other institutions that may not be centers, so that you may have, for a drug study or for some other study, as much as 30 or 40 clinics, and there are only 10 centers.

Williams: Sure. So let me just go back to something. So, when you talk about the centers being important for having a patient population available to do the study, you're really saying that the important word, at this point in sickle cell, is really clinical trials. Running controlled clinical trials to test the effectiveness of different therapies, and that a lot of the "basic" research that would involve patients is not -- I don't want to say it's on the back burner, but maybe the more critical studies at this point, you would say, would be doing the clinical trials?

Castro: I can only tell you what is going on in other diseases. If you look at AIDS, a clinical trial is going on all the time, and in many other diseases, clinical trials. In sickle cell disease, the large, the latest large federally funded trials may have been the stroke problem, which they show that you can prevent stroke, involving 130 patients, so that the basic research could come from the centers or it could come from other places, as the article came from the Veterans Administration. So you never know. But there has to be always a well-structured center with patients and with capability for doing research that you can apply whatever is found in the basic science, both within the centers or outside, to sickle cell disease.

Williams: How difficult is it to recruit patients?

Castro: We haven't had difficulties. The patients trust us. They know who the investigator is. And I think that a lot of other centers don't have any difficulty recruiting either. But if you are not an institution where traditionally there has been a lot of work in sickle cell disease, it's difficult, too.

Williams: So that's one of the areas that you see as being sort of a challenge right now for progression on treatment, just doing more of these clinical trials, controlled studies with large patient involvement. Well, that's interesting. Let me just divert a little bit from my interview questions. Developing treatments. We talked about that. So, this is sort of a personal perspective. What do you think your greatest contribution to sickle cell disease research has been?

Castro: Research.

Williams: Well, we can broaden this a little bit. I mean, you could tell me research first, and then perhaps we could talk about just to the disease overall.

Castro: I don't know. I think that that is best asked of somebody else.

Williams: You do?

Castro: Yes. It's difficult to answer.

Williams: Would it be fairer to ask sort of what has been your kind of personal goal and objective sort of for staying in this field? Like, what would you like to see happen?

Castro: What would I like to see happen? I would like to see more clinical trials. I would like to see more basic research. And because bone-marrow transplantation has shown that it has the potential for cure, I think that a lot of attention should be paid to ways of doing bone-marrow transplantation that would not have the limitations that are currently there. And the limitations are (a) that there are not enough donors. If you use a non-related donor, then all of a sudden the mortality of the transplant becomes very high. Or (b) that perhaps one can do more manipulations of different type of transplants that would not require the sibling or something along this line. So I think that would open up other options. There has always been the possibility that there may be a gene therapy that may make it possible to produce genetically a molecule of hemoglobin, like fetal hemoglobin, or like genetically devised anti-sickling hemoglobin that could be produced to see if that would work. But there are really big challenges in gene therapy for sickle cell disease because of the nature of the product, the gene product, that we want to achieve. It needs to be achieved only in the red cells, and it needs to be achieved in very large quantities.

Williams: And that's an interesting point, because when I think about this disease and I think about the challenges for a cure, and is there something else that is remotely parallel to it? I mean, the fact that you said it is a red-blood-cell disease. It alters the structure of a key molecule. It's so common, but it's so difficult to specifically address the molecular problem with it. Is that a basis for why it's been so "curiously slow"? I mean, ever since I've been reading the literature from the '70s, you have this one body of research saying, "Where is the treatment? Where are the treatments?" and part of the question is, is there something inherent in the basic scientific principles why this is, how this disease works? It's just an incredibly complex disease. It has a number of symptoms.

Castro: Well, the bottom line there is that a modification of one single amino acid causes everything, and if one could reverse that… one has to reverse that. But to achieve that is one of the most difficult challenges in the biology of gene therapy. You can put in a normal gene product, a normal gene into a stem cell, and make it produce . . .

Williams: Normal . . .

Castro: Yes, but only small amounts of the normal product. If it were an enzyme that needed to be corrected, then a small amount would do it. If you're working with hemophilia, a small amount would do it. But in sickle cell disease, you need…

Williams: Quantities.

Castro: So the principle is the same in terms of what needs to be done, but the goal is more difficult to achieve because of the nature of that. Also, if you look at thalassemia, again, there people could be doing gene therapy and so forth and so on. What a lot of people are doing is, at least right now, is bone-marrow transplantation also.

Williams: I see. I'm going to make a note, this whole thing of specificity in quantity, almost sort of this double-edged sword. You need it to be very specific but also able to produce large quantities.

Castro: In the right cells.

Williams: In the right cells, which is part of the specificity challenge. Right? So that's very difficult.I think we've covered most of this. The one thing I don't think I had a very good feel for is sort of the early days with Roland Scott, when you were just beginning to set up the sickle cell center here. What were some of the challenges then?

Castro: Well, we never had enough money to begin with, but that's everybody's challenge. I think that at the time, we were doing other things, like education to prevent sickle cell disease. It seems unfair that people nowadays would have a child with sickle cell disease without ever knowing that they were at risk for having a child with sickle cell disease. That didn't seem right, and so that we and many others were trying to make sure that, through education, people knew. Now, once they know, they can do whatever they want to. They can either have the child or take the risk or not take it, but it shouldn't come as a surprise.

Williams: So you mean people with the trait.

Castro: Right, right.

Williams: So you supported the screening programs?

Castro: Well, yeah, because it just doesn't seem right that having the possibility of knowing whether you're going to have a sick child, be kept from you unless you yourself don't want to know it. Okay? So for that reason, a lot of programs for screening were done and, nevertheless, when the screening program began, everybody has to be tested for sickle cell disease. A number of families with a new baby with sickle cell disease said, "We didn' t know anything about it," and that was a big challenge. Why couldn't we get at least the people to be aware of the disease? There are other communities, such as the Cyprus or Greek community in England, in Sicily, or so forth, in which you could actually see that the birth of babies with thalassemia has gone down because of communication. And I am hard-pressed to say that that is the case for sickle cell disease. So that was a challenge. Now we concentrate on just making sure that everybody knows there is such a thing as sickle cell disease. We do tests free of charge and offer counseling.

Williams: Okay, for people. But at this point, you aren't sure there's been a decrease as a result of the education.

Castro: I see no evidence of that. And I think if anybody had found that evidence, it would have been published.

Williams: Well, that's interesting because , like you said, it certainly is avoidable to people who have the trait. Right?

Castro: Some people may not wish to be bothered with it, life is too complicated, don't bother with this, and that's fine. But other people say, "Look, it was possible for me know it. Why didn't I know it?"

Williams: And then I suppose there's always the probability, right, I mean, even if you do have two people who carry the trait -- what's it, one in four? I don't know the statistics.

Castro: Correct.

Williams: So there is this sense of we'll take our chances, roll of the dice.

Castro: Well, that's fine because I think that it's their right to have children. But it's also the right, if the information is available, to know whether or not they are the couple who's at risk for having a child. It is also the right to know. They may refuse that. They may say, "Don't bother me with it." But at least they should always have the option. The sense that I get from when we look at this was that people still didn't know.

Williams: Really? So, but anyway, in the beginning days, so the challenge was funding, having funds to start the center. Were there any other things in terms of, with Roland Scott, just starting out?

Castro: I can't remember anything very specific about that. We were working then with animal models. Those were low-tech animal models. Now we have high-tech animal models, genetic models, which are much better than what we had then. So I think that there have been a lot of advances. But I always see, wonder whether it couldn't be more advanced if the funding had increased or at least kept up rather than, in my opinion, decreased.

Williams: Yeah. I'm going to definitely look at that because, like I said, I certainly had it in my notes to look at the role of federal funding and what that played on treatment, and I think you sort of reinforced that that's an important issue to look at. I think that, at least in terms of my questions, is really it. We really moved through a lot of the focus that I had here. I don't know if there's anything else you wanted to add at this point?

Castro: Let me just go over this statement. Back in February of this year, I said that the Sickle Cell Anemia Act established the National Sickle Cell Disease Program, promoting disease awareness and provided resources targeted for basic and clinical research. Progress was made primarily through 10 federally funded comprehensive sickle cell centers, one of which was at Howard University. And since this time, important achievements in understanding the disease and developing effective treatment have taken place so that the life expectancy and quality of life of patients are improved, and I listed what I felt to be the five most important treatment developments. Okay? First was that the high mortality in infants with sickle cell disease was reduced by newborn diagnosis. Second, the morbidity and mortality from recurring strokes, a terrible quality of life, which affected 5 to 8 percent of children, has been reduced by the transfusion program, and now even the first stroke can be prevented. Well, that's an advance. The children with sickle cell disease who have a healthy sibling can have bone marrow transplantation, which is a curative procedure, at least in the short run. Then I talked about hydroxyurea. And, fifth, there is increasing recognition that you can use transfusions to treat acute, life-threatening lung involvement, like the chest syndrome, and thus one can decrease the mortality from that complication. That's my extrapolation of what I have seen. There hasn't been a good study on that area, but they're going to come out.

Williams: I see. I think there's no question that's a very good, concise coverage of the major advances, I think, and is an important piece. So you're hoping more is done. You hope that it doesn't sort of plateau right now.

Castro: Well, we recently submitted a grant application to try to become, once more, a federally funded center for the years 2003-2008, so we will not know whether we will be selected, and we won't know it until sometime in late 2002, I think. However, the amount of money that was available for competition was such that the number of projects that will be put in is reduced as opposed to how we used to put in projects.

Williams: Well, and projects are so much more expensive.

Castro: Yeah, much more expensive now than they were before. And the same problem that we have, other universities have.

Williams: Right. Although, I mean, do you really get the impression that outside the centers, I guess this is just not a hot research topic. I mean, if the sickle cell centers have become almost a way of sort of saying we've taken care of the problem with the sickle cell centers, so others need not focus on it, then to a certain extent it's not meeting its initial purpose. And I wonder if it's happening.

Castro: Well, particularly if they are not funded sufficiently. If they are saying, "Well, we are doing something for sickle cell research, we've got 10 centers," but at the same time, the amount of money has become less and less in constant dollars, then, yes, on the one hand you're saying you're addressing the problem, but it could have been addressed better if funding had grown.

Williams: Yeah. Is this a job for political lobbying now, do you think?

Castro: I would think so, but I'm not a political animal, so I don't know. I look at other disorders that have gotten much more funding, and they are certainly very vocal.

Williams: And that's another question. What has been the role of political advocacy in addressing treatment issues? And certainly in the early '70s, there was a loud voice. You had the Black Panthers. They were also doing studies. I think the urgency for Congress to do something was there. We've made some progress, people are happy, quality-of-life issues are better, could still be better, but they're better than they were. So maybe there are other things. Maybe dollars should be spent elsewhere. And so whose job is it really to get the ball back on track for sickle cell?

Castro: That's a difficult problem. It's everybody's job and the political individual who listens to the community. So that we should try to educate the community better to see if we can get a groundswell of support, but I haven't seen it happen. And part of it is because there have been other diseases that have come to the forefront that can affect anybody, and a genetic disease, by definition, you either have it or you don't, so that there is also that particular dynamic, that some people will say, "Let's put the money into something I can catch."

Williams: Right.

Castro: That's just my crude way of saying it.

Williams: Well, there was an article where someone said sickle cell disease is not your cousin's disease. That is, if people in Congress have a cousin or someone like that who's had this disease, it becomes something that's easier to relate to. To the extent that it's not specifically their cousin's disease, it may not have the focus. Let me just ask you, what about the role of the NMA, the National Medical Association?

Castro: I don't know. I have not been involved with them except for a rare invitation to go there and give a talk to them.

Williams: Okay, then. I've seen on the Web site and again, the NMA, I didn't know what their involvement is and what role they could play in this sort of thing, but it was certainly one that came to mind. And, of course, there is the Sickle Cell Disease Association. Again, I don't know what they do. I think, like I said, this was sort of the basis of my questions, and you've answered all of them admirably. So for a person who thought, "I don't have very much to say," you gave me a lot of food for thought, so I appreciate it.

End of Interview